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Neurochemistry of Attention-Deficit/ Hyperactivity Disorder (ADHD)

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I. Introduction

There are numerous books about Attention-Deficit/Hyperactivity Disorder (ADHD) on the market. These books range from being very nontechnical, geared towards elementary educators and parents, to highly technical, geared towards medical and mental health professionals. To complicate matters further, the manner in which ADHD is defined and diagnosed has recently changed with the release of the DSM-V in 2013, which makes even relatively recent texts out-of-date. This Creative Inquiry project involves research into the most recent data on the neurochemistry behind what causes ADHD and comorbid conditions, as well as the neurochemistry of how drugs used to treat these conditions work to affect patient mental health. The goal of this project is to write and publish a book that begins with simple descriptions of these processes and builds to more technical language, providing parents and teachers with the ability to become experts in ADHD without a preexisting background in science.

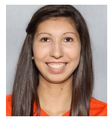
II. Research Team

Mikaela B. Conley
Mikaela Conley is a sophomore microbiology major with a minor in psychology at Clemson University. This is her first year working with the Smith group.

Carter R. Ellis
Carter Ellis is a sophomore Bioengineering major at Clemson University. This is her first year working with the Smith group.

Lloren M. Hile
Lloren Hile is a sophomore nursing major at Clemson University. This is her first year working with the Smith group.

Connor J. Mairena
Connor Mairena is a junior Packaging Science major with a minor in Psychology. He has been researching with the Smith Group for two years.



Sydney L. Moseley
Sydney Moseley is a sophomore biological sciences major with a minor in psychology. This is her first year working with the Smith group.

Thomas J. Wert
Thomas Wert is a sophomore Biological Sciences major with a minor in Psychology. This is his first year working with the Smith group.

III. ADHD in DSM-V: Definition and Diagnosis

The manner in which ADHD is defined and diagnosed has recently undergone significant change with the release of the new *Diagnosis and Statistics Manual V* in 2013. One significant change is that the condition known as "ADD" is no longer a diagnosis that is made. ADHD is now the recognized term for the condition. ADHD can present as one of three subconditions on the basis of which particular symptoms predominate in the patient: Predominantly inattentive, predominantly hyperactivity/impulsive, or combined type. From there the disorder can be classified as either mild, moderate, or severe.

An essential feature of diagnosis is the *persistence* of inattention and/or hyperactivity-impulsivity that *interferes with functioning* of the patient or their development. Furthermore, symptoms and manifestations of the disorder must be present in multiple settings, such as home and school, work, etc.

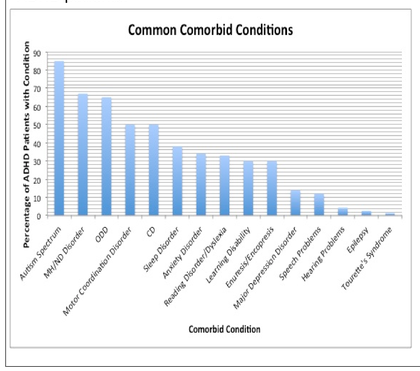
Inattention is viewed as lack of persistence, inability to concentrate on a set task, difficulty with sustaining focus, and being disorganized.

Hyperactivity is viewed as excessive motor activity when it is deemed inappropriate, or excessive fidgeting, tapping or talkativeness.

Impulsivity is known as actions taken or decisions made without forethought that has a high chance of causing harm to the individual.

IV. Comorbid Conditions

The most common statistics indicate that about 65% of ADHD patients have at least one comorbid condition. The graph below displays the frequencies of the more commonly observed conditions in ADHD patients.

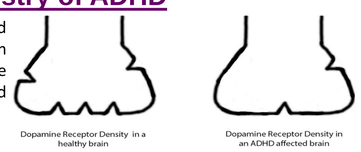


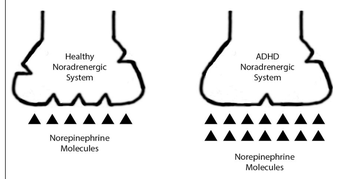
Comorbid conditions lead to an increase in the complexity of ADHD, impacting the symptoms, diagnosis, and prognosis of ADHD. In addition, comorbid conditions increase the difficulty of treatment selection. For the patient, comorbid conditions increase the morbidity and disease burden of ADHD and also may affect patient compliance, leading to further difficulties in treatment.

Analyzing the true correlation/coincidence of ADHD and other conditions is complicated by the additional influence of socioeconomic standing, risk factors in pregnancy (see box VIII), etc.

V. Neurochemistry of ADHD

Dopamine plays a role in memory and reinforcement (see image to the right) but in ADHD patients, Dopamine Transmission levels are found to be decreased, causing inattention and difficulty in memory formation.





Norepinephrine is also involved in cognition and behavior, but the receptors for norepinephrine are much less efficient in ADHD patients' brains than healthy brains (see image to the left). This leads to poor neuron function, leading to impulsivity and inattention.

Serotonin is a key component in controlling impulsivity and the ADHD brain has a decreased number of serotonin receptors (see image to the right), leading to hyperactivity and impulsivity.

VI. Treatment Options

There are both medicinal and non-medicinal treatment options for ADHD, with medicinal options being much more common and offering much more consistent results.

FDA approved medications for ADHD are broken down into stimulants and non-stimulants:

Stimulants:
- Methylphenidate (*Ritalin)*- The most common psychoactive stimulant prescribed, it is believed to work by inhibiting the dopamine transporter (see box V, upper figure) in the presynaptic cell membrane, blocking its reuptake, causing an increase of dopamine in the synapse
- Amphetamine *(Adderall)*- Believed to work through increasing levels of neurotransmitters, including dopamine and norepinephrine, in the synapse by causing the release of newly synthesized cytosolic dopamine from the nerve terminal

Non-stimulants:
- Atomoxetine (*Strattera)*- a specific presynaptic inhibitor of norepinephrine reuptake (see box V, middle figure), increasing the levels of the neurotransmitter in the synapse
- α-2 Agonists (*Kapvay and Intuniv)*- inhibit the release of the norepinephrine neurotransmitter (see box V, middle figure), which decreases the body's state of arousal

Non-medicinal options:
- Behavioral therapy, cognitive therapy, neurofeedback, modifying diet/nutrition, and increasing exercise

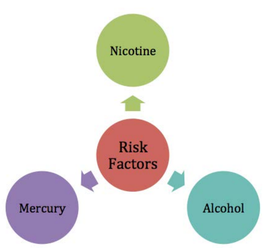
VII. Genetics

Genetic factors and biochemical abnormalities play considerably large roles in the etiology of ADHD. Several molecular genetics studies have demonstrated that deficiencies in the serotonergic and dopaminergic systems (see box V) are associated with brain abnormalities that cause major symptoms of ADHD. Two dopamine candidate genes have been identified through numerous genetic studies and show a strong association with the neuropsychiatric disorder ADHD when expressed, specifically the dopamine transporter gene (DAT1) and the dopamine receptor gene (DRD4). Impaired dopamine transmission has a strong correlation with typical ADHD symptoms such as hyperactivity, inattention, and impulsivity. There is currently substantial evidence that links several genes coding for DRD4, DAT1, 5-HTT, DRD5, and HTR1B to the etiology of ADHD.

Dopamine Genes
- This DRD4 gene is expressed in the frontal lobe region of the brain and is involved in the dopaminergic system (see box V) and affects functions like language processing, memory, and attention.
- The association between a 48 base-pair repeat polymorphism of exon III of the DRD4 gene and ADHD is the most consistent and replicated molecular genetic finding in ADHD.

VIII. Pregnancy and Risk Factors

ADHD can be caused by a variety of genetic and environmental factors, including prenatal factors to which the fetus is exposed before birth. Recent studies have concluded that nicotine, alcohol, and mercury exposure in utero may lead to development of ADHD later in life. It is important to note that these studies have shown a correlation, but not necessarily a causative effect between these substances and the onset of ADHD. It is possible that these substances are part of larger environmental and genetic (See box VII) components and do not impair fetal development on their own. Either way, it is essential for mothers to be informed on these issues and how their actions can affect their child's mental development. This appears to be an area requiring significant additional research.



IX. Conclusions

The recent changes with respect to how professionals define and diagnose the condition of ADHD were the primary motivation for this study. It is important to evaluate the most up-to-date information related to ADHD across a range of scientific disciplines and to cast all the previous studies in light of the new definitions. Although we have only been exploring available scientific data for a about two months for this project, a notable challenge we have faced is the inconsistency of study parameters and the complexities involved in analyzing studies on human subjects to extract meaningful, clear conclusions. We hope to continue a detailed analysis of available original research studies in an effort to reveal clear understanding of the science behind ADHD and treatment options for so that non-experts can make educated assessments related to the condition.

Funding

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